RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

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Prevention Program Averts Initiation of Alcohol and Tobacco Use

Communities That Care aids towns in choosing and implementing effective activities.

BY SHARON REYNOLDS,
NIDA Notes Contributing Writer

In the first randomized trial of Communities That Care (CTC), middle school students in towns that utilized the prevention system reported less delinquency, initiation of alcohol and tobacco use, and binge drinking than peers in comparison towns. Students in test towns also reported lower rates of current alcohol and smokeless tobacco use in the eighth grade.

CTC provides training and materials to help communities organize coalitions; identify risks for youth drug use and delinquency, as well as protective factors in the community; choose interventions with proven effectiveness; and implement the interventions with fidelity. Communities in Canada, the United Kingdom, the Netherlands, Germany, and Australia, as well as the United States, have adopted CTC. However, the current trial, called the Community Youth Development Study (CYDS), is the first to randomly assign communities to implement either CTC or prevention as usual. Earlier analyses of the data showed that CTC improved communities' coalition building, as well as their selection and implementation of evidence-based prevention programs. It also reduced the prevalence of factors associated with youth substance abuse. The new findings establish that CTC achieved its ultimate goal of preventing behaviors that pose a risk to health.

Students engage in a "mat chat" on bullying through an after-school program chosen by community leaders under the guidance of the Five Town CTC (see box, page 12).

Photography by Peter N. Russell

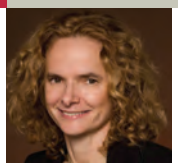
TRAINING COMMUNITIES IN PREVENTION SCIENCE

The CTC program was designed by Drs. J. David Hawkins and Richard F. Catalano of the Social Development Research Group at the University of Washington. "We wanted to help communities use prevention science to guide their actions," explains Dr. Hawkins. "Prevention science tells us that if you want

[*Continued on page 12*]

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*



Physical Activity May Prevent Substance Abuse

From the minute they arrive at the park, children move constantly. They run, jump, chase, and climb. Wrapped up in their fun, they aren't thinking about the health-promoting effects of exercise. But NIDA scientists are. Staff scientists are considering the possibility that exercise—including active play, outdoor adventure, team sports, martial arts, and dance—not only boosts energy and keeps weight in check but also helps prevent substance abuse. NIDA has already invested over $4.3 million to spur research on this emerging area of addiction science.

Although people tend to think of exercise as good for the body, it also benefits the brain. As it invigorates the heart and lungs, it stimulates the brain's reward pathway and heightens mood-boosting neurochemicals. Animal research indicates that exercise promotes the formation of blood vessels in the brain, forges connections between cells, enhances repair of neural tissue, and generates new neurons in memory-formation areas. Through its actions on hormones that affect the nervous system, exercise also improves an animal's tolerance of stress—an observation that is particularly intriguing given the links between stress and drug abuse.

Such observations may explain why competitive runners experience mood elevations, physical activity sometimes relieves mild depression, and older people who exercise improve in both mood and cognitive function.

Patterns of drug abuse among teens suggest that physical activity can strengthen resistance to addiction. Results from the NIDA-funded Monitoring the Future survey, for example, indicate that high school students who exercise regularly are less likely than sedentary teens to smoke cigarettes or abuse marijuana ("Lower Rates of Cigarette and Marijuana Smoking Among Exercising Teens," *NIDA Notes*, Volume 22, Number 4, page 20). The relationship between drugs and exercise, however, may be indirect. Perhaps students who choose to exercise tend to make healthy decisions in general. Initiation of substance abuse may also be countered by the support of teammates, coaches, and family; by other social aspects of participation in organized activities; and by the time management skills that active teens develop .

Apart from improving the health of the developing brain, there are many reasons to think that physical activity can be a useful means for preventing substance abuse among young people. The best way to grab the attention of children and teens is often to offer them a range of appealing challenges. Physical activities—particularly in natural environments—offer youth healthy opportunities to learn skills, take risks, and achieve goals.

I run 6 miles a day because I enjoy it. But, as a neuroscientist, I'm intrigued that physical activity is good for the brain. At NIDA, we look forward to supporting groundbreaking research on the neurobiological, psychological, and social processes by which exercise may promote overall well-being and protect against drug abuse and addiction. ■

NIDA Notes

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Prevention Program Reduces Later Risky Sexual Behaviors

Teens who participated in the school-based drug abuse prevention program Project ALERT were less likely than peers to engage in risky sexual behaviors as young adults, report NIDA-funded researchers. Dr. Phyllis L. Ellickson and colleagues at RAND Corporation queried 1,901 unmarried, sexually active 21-year-old men and women from Midwestern communities. The participants had attended schools randomly assigned to use Project ALERT, a middle school curriculum that motivates young people to abstain from drug use and teaches resistance skills; Project ALERT plus 10 booster lessons during high school; or no special program.

Forty-four percent of those exposed to either the core or expanded version of Project ALERT reported that they had had multiple sex partners during the past year, compared with 50 percent of their unexposed peers. Just 27 percent of the Project ALERT participants reported that they had engaged in unprotected sex while under the influence of alcohol or illicit drugs, as opposed to 32 percent of the control group. The results suggest that school drug abuse prevention programs can reduce at least some risky sexual behavior years later.

> Journal of Adolescent Health 45(2):111–117, 2009.

Menthol May Strengthen Nicotine Addiction

In a recent NIDA-supported study, Latino and African-American smokers of menthol cigarettes benefited less from a 1-month smoking cessation program than did smokers of nonmenthol cigarettes. During the month following the treatment, only 23 percent of Latinos and 30 percent of African-Americans who smoked menthol cigarettes achieved a weeklong period of abstinence, compared with roughly half of the nonmenthol smokers in each group. Caucasian participants showed no gap in abstinence rates between smokers of menthol and of nonmenthol cigarettes.

Study leaders Drs. Kunal K. Gandhi and Jill M. Williams at the University of Medicine and Dentistry of New Jersey also found that in each ethnic group, menthol's negative impact on quitting success was most pronounced among participants of low socioeconomic status. The researchers hypothesized that smokers who can afford only limited cigarette purchases may prefer menthol cigarettes because menthol's soothing effects on the throat enable them to puff more deeply or frequently and thus extract more nicotine from each cigarette. In earlier work, the New Jersey group had shown that smokers of menthol cigarettes absorb higher levels of nicotine than smokers of nonmenthol brands, which may increase the severity of addiction and the difficulty of quitting. Of the 1,688 participants in the recent study, 46 percent smoked menthol cigarettes, including 81 percent of African-Americans, 65 percent of Latinos, and 32 percent of Caucasians.

> International Journal of Clinical Practice 63(3):360–367, 2009.

Brain Responds to Marijuana Cues in Familiar Manner

Cravings triggered by marijuana-related cues, such as a marijuana pipe, are associated with a pattern of brain activity similar to that which accompanies cravings for other drugs, say NIDA-funded researchers at the University of New Mexico. Dr. Francesca M. Filbey and colleagues obtained functional magnetic resonance images of reward areas in the brains of 38 regular marijuana smokers while the participants handled either a marijuana pipe or a neutral object, in this case a pencil, after going 3 days without the drug. While handling the pipe, the study participants reported more craving for marijuana, and the brain images revealed greater activity in the ventral tegmental area, nucleus accumbens, prefrontal cortex, and other reward- and motivation-related areas. In other studies, activation of these neural pathways has been associated with cravings for alcohol, nicotine, and cocaine; the intensity of activation is considered an indicator of the severity of dependence on those drugs.

As with other addictive drugs, the extent of the cue-induced activity in the brains of the marijuana smokers correlated with the number of problems that the participants reported, such as family troubles, work missed, or jobs lost. According to the researchers, the findings suggest that medication development strategies targeting these areas of the brain may ultimately prove effective against craving and addiction to marijuana, as well as other drugs.

> Proceedings of the National Academy of Sciences 106(31):13016–13021, 2009.

CORRECTION: The article titled "Study Supports Methadone Maintenance in Therapeutic Communities" (*NIDA Notes*, Volume 23, Number 3, page 8) should have attributed a 2005 national survey of 380 therapeutic communities to the Institute for Behavioral Research at the University of Georgia.

HIV Treatment Interruption Is Pervasive After Release From Texas Prisons

Helping inmates fill out application forms for antiretroviral medication doubles prescription utilization.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Nearly all Texas state prisoners who receive antiretroviral therapy while incarcerated experience some treatment interruption following their release, according to a new NIDA-funded study by Dr. Jacques Baillargeon of the University of Texas Medical Branch in Galveston. More than two-thirds of these interruptions last longer than 60 days, during which time ex-prisoners may develop higher viral loads that increase their risk of disease progression and transmission to others.

These results highlight a national public health problem, according to Dr. Baillargeon, who notes that prison discharge planning and community-based HIV care in Texas is similar to that in other states. The study also indicated that simply helping prisoners with the paperwork necessary to obtain free federally funded antiretroviral therapy can substantially reduce treatment interruptions.

A TIME OF INCREASED RISK

Because rates of HIV infection among inmates are currently several-fold those of the general population, U.S. prisons have become focal sites in efforts to control the virus. Although most HIV-infected inmates receive antiretroviral therapy during incarceration, many have extremely limited access to health care systems in the months immediately following their release, Dr. Baillargeon says. As a result, they confront obstacles to continuing treatment at the same time they face expanded opportunities to initiate or resume injection drug use, unprotected sex, and other HIV risk behaviors. Along with the risks of disease progression and transmission, discontinuation of antiretroviral therapy may lead to medication-resistant HIV.

To examine medication use among recently released inmates, Dr. Baillargeon and colleagues collaborated with the Texas Department of Criminal Justice, which oversees one of the largest state prison systems in the United States. Texas administers a federally funded program, the AIDS Drug Assistance Program (ADAP), to help ex-prisoners continue their antiretroviral treatment during the time it takes them to locate treatment services in the community. During standard discharge planning, HIV-infected inmates receive a four-page application form for a free 30-day supply of the medication through ADAP, along with a 10-day supply of antiretroviral medication and information on accessing community HIV treatment.

Partway through the 4-year study, Texas prisons phased in a new discharge program (see box, page 5) for inmates with HIV. Coordinators succeeded in providing 55 percent of those eligible with formal assistance in completing and submitting the ADAP application.

Although most HIV-infected inmates receive antiretroviral therapy during incarceration, many have extremely limited access to health care systems in the months immediately following their release.

ASSISTANCE INCREASES FULFILLMENT

The researchers examined all prescriptions in the Texas ADAP database. They found that about 5 percent of released inmates filled the initial 30-day prescription during the first 10 days after their release, and 18 percent did so during the first 30 days. Inmates who received assistance from a caseworker to complete and submit the ADAP application filled their prescriptions at rates about double those who did not receive the help. At 60 days after release, those who had received assistance continued to show an advantage—34 percent versus 26 percent.

Although similar percentages of each ethnic group received assistance with the ADAP, Hispanic and African-American participants were less likely than whites to continue antiretroviral treatment during the first 10 and 30 days after release. Those disparities disappeared, however, by 60 days.

Individuals not on parole filled the

Texas Prison Discharge Planning for Inmates With HIV

Prisons in Texas adhere to a specific plan for releasing inmates with HIV. Thirty days before the release of any inmate, the prison notes whether he or she is receiving antiretroviral therapy. On the day of release, those who have been on the therapy receive:

- A copy of recent HIV laboratory test results
- A 10-day supply of antiretroviral medication
- A list of clinicians who provide care to patients with HIV in the released inmate's home community
- An application to the AIDS Drug Assistance Program (ADAP) to receive a 30-day supply of antiretroviral medication; and, if resources permit, assistance in completing and submitting the form
- An ADAP medication certification signed by a physician
- A toll-free phone number and instructions to call an ADAP caseworker for assignment to a local pharmacy.

Although the federally funded ADAP program has eligibility requirements that include an inability to pay for medications, the Texas Department of Corrections found that virtually every inmate leaving its prison system qualifies.

initial antiretroviral prescription within 30 and 60 days of release at lower rates than parolees, who had parole officers to encourage them, says Dr. Baillargeon. Furthermore, participants whose HIV infection was under control in prison, as indicated by an undetectable viral load, were more likely to fill the initial prescription than those with measurable amounts of HIV in their blood. Dr. Baillargeon notes that some individuals, while in prison, are better than others at adhering to antiretroviral regimens, and that this difference in behavior may continue after release.

Among those who filled the initial 30-day prescription through ADAP, only 6 percent accessed the medication for a second month without interruption. This finding suggests that former inmates with HIV may need additional assistance coordinating their health care during the first few months after release.

The study included 2,115 inmates with HIV released between January 2004 and December 2007. Of the participants, 83 percent were male, and 58 percent had committed a drug-related crime. The study population was 60 percent African-American, 27 percent white, and 13 percent Hispanic. Although demographic characteristics of prison inmates vary from state to state, Dr. Baillargeon says that he expects the study results to apply across the Nation.

In a subsequent analysis of clinical data from 1,750 HIV-infected inmates returning to the community in one Texas county, Dr. Baillargeon and colleagues found that only 20 percent of former inmates enrolled in an HIV clinic within 30 days of release. Only 28 percent did so within 90 days. At both assessment times, those who received enhanced discharge planning were about 50 percent more likely than those who did not to enroll in a clinic, suggesting that enhanced discharge programs may increase continuity of HIV care among newly released inmates.

"Our findings document that a low percentage of former prisoners access antiretroviral therapy in a timely fashion after release. This observation may underlie the results of prior studies that reported loss of both immune function and viral suppression among offenders who return to the criminal justice system," says Dr. Baillargeon.

A STEP IN THE RIGHT DIRECTION

The results of the study spurred the Texas Department of State Health Services to hold a summit on antiretroviral therapy continuance after prison release. Summit participants, including Dr. Baillargeon, proposed additional steps public health officials might take—for example, providing transportation assistance or vouchers to facilitate released prisoners'

contact with health care providers. In future research, Dr. Baillargeon's team plans to identify psychosocial and practical barriers that prevent former prisoners from accessing antiretroviral therapy. The team's goal is to develop interventions to remove such obstacles.

"This collaboration between the researchers and the Texas Department of Criminal Justice represents a step in the right direction toward fighting the HIV epidemic, and NIDA applauds their effort to address an important public health problem for the Nation," says Dr. Dionne Jones of NIDA's Division of Epidemiology, Services and Prevention Research. Because helping inmates complete and submit the ADAP forms was inexpensive, such assistance may prove a cost-effective and valuable component of efforts to improve medication continuance.

"Followup care after release might further enhance the proportion of former prisoners with HIV who continue medication," says Dr. Jones. "Former prisoners often face many difficulties—including family estrangement, unemployment, lack of housing and transportation, and vulnerability to drug relapse—as they try to re-integrate into the community."

NIDA recently expanded its own efforts to fight HIV among prisoners. The Institute, along with the National Institute of Mental Health and the National Institute of Allergy and Infectious Diseases, is newly supporting 12 research teams as they examine ways to identify persons with HIV within the criminal justice system and link them to effective therapy during periods of incarceration and after community re-entry. Over the next 5 years, the teams will compare different methods of identifying HIV-positive offenders and engaging and retaining them in treatment. Some of the projects will create and compare systems to better integrate and coordinate HIV management efforts. The grants will also support randomized controlled trials among large groups of HIV-positive parolees and probationers, comparing various approaches for linking them to treatment and social services in their communities. ■

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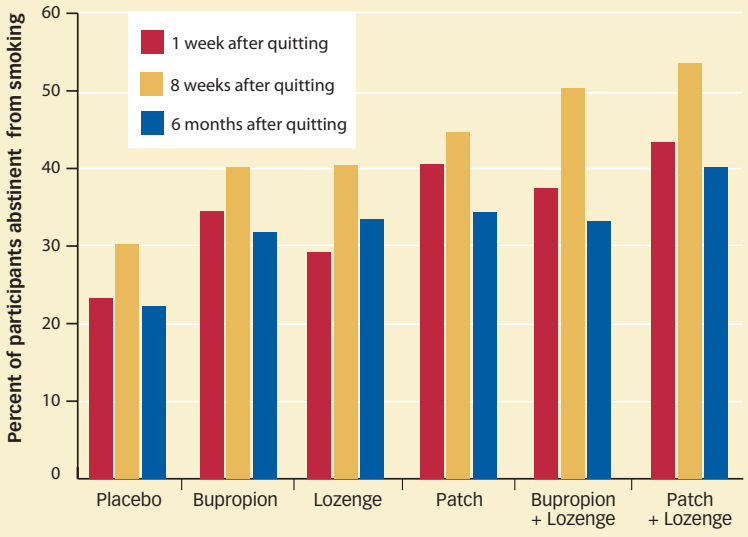
Combination Therapy Most Effective for Helping Smokers Quit

Treatment with a nicotine patch and lozenge outperformed four other smoking-cessation therapies in a large clinical trial.

BY SHARON REYNOLDS,
NIDA Notes Contributing Writer

MANY THERAPIES REDUCE SMOKING Abstinence rates for all treatments peaked at the 8-week assessment. Abstinence was confirmed by breath carbon monoxide levels measured during visits to the clinic.



In a randomized clinical trial of five smoking-cessation treatments, a combination of the nicotine patch and nicotine lozenge produced the greatest benefit, relative to placebo treatment, in helping people quit smoking and remain abstinent for at least 6 months. Current public health guidelines, based on earlier clinical trials testing individual smoking-cessation aids, recognize that several medications increase smokers' success in kicking the addiction. However, the lack of direct comparisons between smoking-cessation aids has made it difficult for doctors and smokers to choose one treatment over another.

At the start of the study, for example, there had been only one placebo-controlled trial of the lozenge's effectiveness, and the combinations of lozenge plus either nicotine patch or bupropion had never been tested in a clinical trial. The patch, used alone, is currently the most common smoking-cessation aid.

FIVE TREATMENTS TESTED

Researchers at the University of Wisconsin's Transdisciplinary Tobacco Use Research Center designed a comparative effectiveness trial "to permit more-informed decisions about the selection and use of smoking-cessation pharmacotherapies," explains study leader Dr. Megan E. Piper.

In the trial, the researchers tested five treatments side by side to see how each performed relative to a combined placebo group that included a matching placebo for each of the five treatments tested. The participants were 1,504 adults who had smoked more than nine cigarettes a day, on average, for at least the past 6 months. They all wanted to quit and had already tried to do so an average of five to six times. The smokers were, on average, moderately dependent on nicotine, according to the Fagerström Test, which is commonly used to measure nicotine dependence. Each participant was randomly assigned to receive either one of five smoking-cessation regimens—the nicotine lozenge, the nicotine patch, bupropion, the nicotine patch plus the nicotine lozenge, and bupropion plus the nicotine lozenge—or a placebo treatment designed to mimic one of the five regimens. Neither the participants nor the study staff were told who was receiving the active treatments. Varenicline (Chantix), a more recently introduced smoking cessation aid, was not included in the study.

The patients began using bupropion and the bupropion placebo 1 week before their chosen quit date and the other therapies and their respective placebos on the quit date. All the treatment regimens continued for 8 weeks after the quit date except for use of the nicotine lozenge and lozenge placebo, which continued for 12 weeks. All participants received two smoking-cessation counseling sessions before the quit date, one session on the quit date, and three additional sessions

during the following 4 weeks.

Most of the patients in every group avoided smoking for at least 1 day during the week following their quit dates, but those receiving the active medications did so at higher rates than those on placebos. The patients assigned to three of the active regimens—the patch plus lozenge, bupropion plus lozenge, and the patch alone—were most likely to be abstinent on day 7 and at the end of the 8-week treatment period (see graph, page 7).

The combination of nicotine patch plus lozenge appears to afford smokers the highest chance of quitting.

At the 6-month followup interviews, however, only the group using the patch plus lozenge had a significantly higher prevalence of abstinence than the placebo recipients, 40 percent versus 22 percent. The patch plus lozenge combination also stood out as being one of two regimens—with bupriopion plus lozenge—that significantly increased, relative to placebo, the number of days from the quit date to relapse, which was defined as smoking on 7 consecutive days. All the active medication regimens except the lozenge alone lengthened the interval between lapsing, defined as taking a first puff on a cigarette after a period of abstinence, and relapsing. This latter finding suggests that continuing medication after a lapse may reduce the chance of a relapse.

Dr. Piper and colleagues note that if they had used the criteria employed by studies that compare a single treatment with placebo, all of the active treatments would have been deemed to outperform the placebos at all time points, with the exception of the lozenge at 1 week after the quit date. However, only the combination of nicotine patch plus lozenge provided a significant advantage under the stringent statistical criteria that are appropriate in studies making multiple comparisons. This suggests that the combination of nicotine patch plus lozenge affords smokers the highest chance of quitting.

EFFECTIVENESS ACROSS THE BOARD

The superiority of the patch plus lozenge combination seen in this trial has several potential explanations, says Dr. Piper. One is that this combination therapy provides two different ways to tackle withdrawal—a steady dose of nicotine from the patch plus the as-needed lozenge to help with transient, strong cravings or challenges induced by an environmental cue. "Alternatively, the effect may be due primarily to the higher nicotine dose from the two mechanisms of administration," she explains.

Dr. Piper says that although the patch plus lozenge showed the best results relative to placebo, the quit rates in all groups—including those receiving a placebo—were unusually high for a smoking-cessation trial. She speculates that this might be attributed to the counseling, which may have been particularly effective, or to the high motivation of the participants, given that they had agreed to be part of a 3-year clinical study of the physical and psychological consequences of smoking cessation.

Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse says, "This is an important study for clinicians because there is evidence about the best of those five treatments. Based on these results, if I have a patient who wants to quit smoking, of the five treatment choices, I would try my patient first on the patch plus lozenge."

"This study provides a better understanding of what these treatments can do," adds Dr. Piper. "To clinicians who think that they don't have anything to help treat smoking, here's some evidence that there's a lot out there that they can use." ■

SOURCE

Piper, M.E., et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Archives of General Psychiatry* 66(11): 1254–1262, 2009.

Cocaine Alters Production of Hundreds of Proteins

Affected proteins include enzymes that influence DNA repair, cell death, stress resistance, metabolism, and aging.

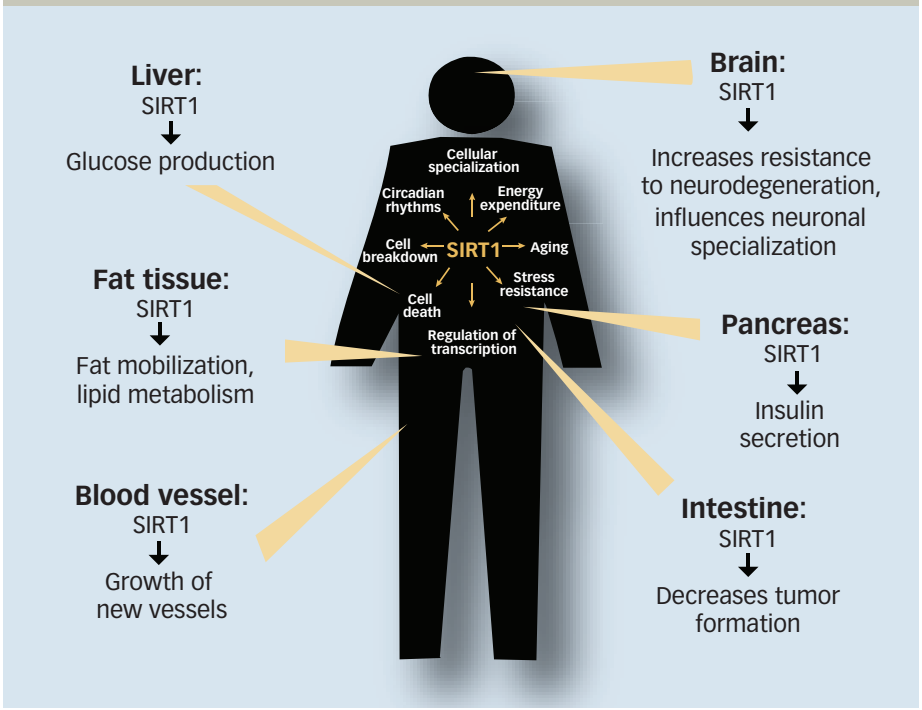
BY LORI WHITTEN,
NIDA Notes Staff Writer

Chronic cocaine abuse may alter the production of more than 1,000 proteins in the neurons of the brain's reward system. The finding by NIDA-funded researchers sets the stage for new advances in understanding how the stimulant causes addiction. Each affected protein may contribute to the cognitive and behavioral changes that mark the transition from voluntary to compulsive drug taking and provide a lead to new anti-addiction medication strategies.

Although some of the proteins identified in the study have previously been linked to cocaine's effects, the great majority have not. Among the most intriguing of these, the researchers say, are two enzymes in the large family called sirtuins. In experiments with mice, chemically boosting the activity of these enzymes intensified drug seeking.

A POWERFUL FAMILY OF ENZYMES IMPLICATED IN COCAINE'S EFFECTS

Sirtuins—also called SIRTs, for "silent information regulators of transcription"— influence a wide range of functions essential for life. This family of enzymes regulates biological processes including metabolism, DNA repair, cell specialization and death, stress resistance, and tumor growth. Sirtuin activity has been linked to longevity in worms and fruit flies. Scientists have thus far identified seven sirtuins in mammals, and SIRT1 has been studied most extensively. Cocaine regulation of sirtuin appears to be specific to one brain region.



ABUNDANT AND SUGGESTIVE FINDINGS

Dr. Eric Nestler of Mount Sinai School of Medicine and colleagues at the University of Texas Southwestern Medical Center and Florida State University used a technique called chromatin immunoprecipitation (ChIP)-chip (see box, page 11) to assess cocaine's impact on the genes for 20,000 proteins in neurons of the brain area called the nucleus accumbens (NAc) of mice. The results indicated that about 5 percent of the genes were more active—likely accelerating manufacture of their protein products—following a week of exposure to cocaine, as compared with a week of exposure to saline. In a smaller—but still ample—number of other cases, cocaine reduced gene activity.

The researchers singled out a pair of sirtuins, SIRT1 and SIRT2, as being of particular interest. Sirtuins regulate basic biological processes in organisms as diverse as bacteria and humans. Although little is known about the sirtuins' function in the nervous system, their involvement in a broad range of fundamental processes suggests that the cocaine-induced increases in levels of SIRT1 and SIRT2 might play important roles in addiction.

Spurred by this suggestion, Dr. Nestler and colleagues investigated the relationship between sirtuins and behavioral responses to cocaine. They administered the stimulant to mice in one chamber of a split cage until the animals began to spend most of their time there, seeking the drug. The researchers then removed the mice

One Protein's Dual Role in Addiction

Chronic exposure to stimulant drugs introduces many changes in the brain's reward system. Some are pathological and others appear to be countermeasures to restore neural health. Recently, Dr. Eric Nestler of Mount Sinai School of Medicine, New York, with colleagues at the University of Texas Southwestern Medical Center at Dallas revealed how one protein that has long been implicated in the development of addiction to stimulants, such as amphetamines and cocaine, also may contribute to a compensatory effect.

The protein, ΔFosB, is a transcription factor, one of a family of molecules that attach to a gene and accelerate or retard production of its protein. In previous work with animals, Dr. Nestler and others established that chronic exposure to cocaine or amphetamine causes ΔFosB to accumulate in the brain region called the striatum. This accumulation correlates with increased drug-seeking behaviors, likely by causing excesses or shortages of proteins in the nucleus accumbens and other areas of the striatum that support cognition and shape reward-related behaviors.

The net result of ΔFosB buildup in the striatum is deleterious, and scientists suspect that it may be pivotal in the transition from initial stimulant abuse to addiction. However, the effect on one protein, c-Fos, opposes amphetamine's impact.

Like ΔFosB, to which it is related, c-Fos is a transcription factor whose abundance in the striatum correlates with behavioral responses to stimulants. In contrast to ΔFosB, which responds minimally to acute drug abuse and accumulates in chronic abuse, c-Fos exhibits a different arc: Its levels rise sharply after acute stimulant exposure and wane during chronic abuse. To Dr. Nestler, these observations suggest that ΔFosB suppresses c-Fos production. The recent development of ChIP technology (see box, page 11) enabled him and his colleagues to test this proposition.

The researchers administered daily injections of amphetamine or saline to rats for a week followed by 5 days of withdrawal—a time when c-Fos reached its lowest level in striatal neurons of the animals that had received the drug. The team then used ChIP to measure ΔFosB binding to the promoter region of the gene for c-Fos. They observed that:

- More ΔFosB attached in the animals given the drug than those given saline;
- Increased amounts of bound ΔFosB correlated with reduced c-Fos production, as evidenced by lower levels of c-Fos messenger RNA;
- The ΔFosB attracted an enzyme called histone deacetylase 1 (HDAC1) that causes DNA to be held more tightly against its protein scaffolding, resulting in less production of c-Fos;
- Increasing ΔFosB in drug-naïve rats reduced the production of c-Fos in response to a single injection of amphetamine.

The researchers concluded that ΔFosB attenuates c-Fos manufacture by attracting HDAC1 to the promoter region of the *c-Fos* gene. "In response to repeated amphetamine exposure, brain cells mount a counter-response that reverses acute amphetamine's increased production of c-Fos," says Dr. Nestler.

Another ChIP experiment revealed a second adaptive response to chronic amphetamine exposure that reinforces the suppression of c-Fos production but is independent from that of ΔFosB. At a location in the *c-Fos* gene promoter region near to that where ΔFosB accumulates, an enzyme called a histone methyltransferase gathers and reduces access to DNA by causing a tightening similar to that observed with HDAC1.

"Dr. Nestler's findings point to a new pathway involving ΔFosB and represent a first step toward determining how this protein represses gene activity," says Dr. John Satterlee of NIDA's Division of Basic Neuroscience and Behavioral Research. "Moreover, they show that histone methylation—an established mechanism underlying changes in gene expression—plays a role in the brain's response to chronic amphetamine exposure."

Dr. Nestler plans to further examine how ΔFosB and c-Fos influence drug seeking and the process of addiction. He also emphasizes that ΔFosB's ability to activate some genes but inhibit others highlights the need to identify examples of both types of actions in the regulation of addictive behaviors.

Like some of the brain's other molecular responses to drugs, ΔFosB augmentation represents an exaggeration of a normal response to natural rewards such as food. "From an evolutionary perspective, accumulation of ΔFosB after natural rewards was probably adaptive," Dr. Nestler says. "It likely helped form memories for food and mates and enhanced motivation to seek these rewards again. Drugs induce an excessive amount of ΔFosB and usurp this process."

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Wallace, D.L., et al. The influence of DeltaFosB in the nucleus accumbens on natural reward-related behavior. *Journal of Neuroscience* 28(41):10272–10277, 2008.

COCAINE ALTERS

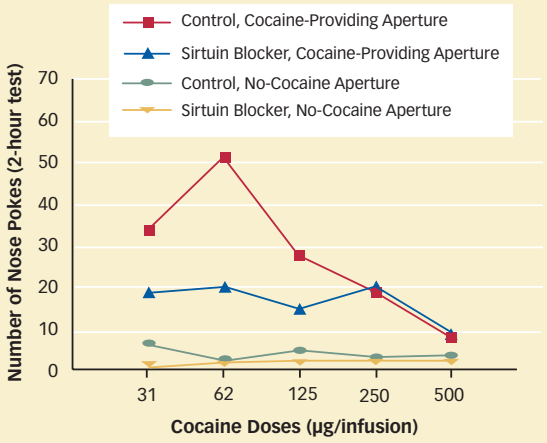
from the cage and infused directly into the NAc either resveratrol, a chemical that increases sirtuin activity; sirtinol, which blunts it; or an inert substance. During subsequent testing in the split cage, the resveratrol-treated mice spent twice as much time, and the sirtinol-treated animals spent half as much time, in the cocaine-associated chamber, compared with the animals in the control group. The researchers concluded that sirtuins intensify cocaine seeking in chronically exposed animals.

The results of that experiment suggested that sirtuin-inhibiting compounds might help people addicted to cocaine overcome their craving for the drug. In a preliminary test of this idea, the researchers examined whether sirtinol reduces the amount of cocaine that animals will self-administer. They infused sirtinol directly into the NAc of some rats and an inert substance into the NAc of others, then allowed the animals to self-administer cocaine by poking their noses into an aperture in a cage wall. At the dose of cocaine that showed the largest effect, the sirtinol-treated rats poked less than half as often as the control animals.

Dr. Nestler and colleagues are now investigating the molecular basis of sirtuins' influence on the brain's reward system.

Dr. Nestler and colleagues are now investigating the molecular basis of sirtuins' influence on the brain's reward system. Experiments using brain slices show that augmenting sirtuin activity—as cocaine does by increasing the enzyme's abundance—boosts the excitability of certain neurons, an effect that is likely to heighten animals' drug seeking. Research now under way is examining the influence that these changes in neural activity might have on drug-related behaviors.

SIRTUIN BLOCKER REDUCES RATS' MOTIVATION TO SEEK COCAINE Sirtinol, a compound that inhibits sirtuin enzyme activity, decreased drug seeking among rats trained to poke their noses into an aperture to receive infusions of cocaine.



DISCOVERY SCIENCE

The use of ChIP-chip to identify hundreds of proteins whose abundance may be altered by cocaine is an example of discovery-based science, in which researchers analyze large volumes of experimental data in search of unanticipated correlations that they can use to create new hypotheses. "My colleagues and I had not expected to see a connection between sirtuins and cocaine exposure, and we knew of no information in the scientific literature that would have predicted such a link," says Dr. Nestler. He and colleagues are also examining the consequences of altered production of many of the other proteins identified in their study.

"Biomedical science advances when researchers better understand the mechanisms underlying illnesses," says Dr. Nestler. "Brain diseases are complex and challenging to understand, but fundamental insights into the ways that cocaine and other drugs alter the brain may lay the groundwork for the development of medications."

"The ChIP-chip technique is all about discovering new targets related to a disease or environmental exposure," says Dr. John Satterlee of NIDA's Division of Basic Neuroscience and Behavioral Research. "The discovery approach lets the organism tell investigators what is important to study, and the sirtuin findings are a great example of that approach's value to science." ■

ChIP and ChIP-chip at a Glance

These techniques, which can be applied to living cells, examine locations where gene-regulating proteins interact with DNA to activate or silence genes, an early step in protein production. Scientists use the methods to learn the details of gene regulation and to detect increases and decreases in activity among genes. With chromatin immunoprecipitation (ChIP), scientists examine a particular gene, whereas ChIP-on-chip (ChIP-chip) can be applied across the entire genome.

SOURCE

Renthal, W., et al. Genome-wide analysis of chromatin regulation by cocaine reveals a novel role for sirtuins. *Neuron* 62(3):335–348, 2009.

PREVENTION PROGRAM
[*Continued from page 1*]

to prevent behaviors such as drug use, you need to address the risk factors for those behaviors in the community and strengthen protection in the community as well. Communities That Care provides stakeholders with tools to assess risk and protective factors in their communities, as well as a menu of tested and effective prevention strategies. Equipped with this information, they can map the profile of risks to which their kids are being exposed and select programs that best address those factors."

Participants in the recent study, which Dr. Hawkins led, were selected from 24 small towns in Colorado, Illinois, Kansas, Maine, Oregon, Utah, and Washington that had not yet implemented evidence-based prevention programs. The researchers randomly assigned half the towns to receive CTC training and implementation assistance and the rest to serve as prevention-as-usual controls. Six training sessions over the course of a year were provided to stakeholders in the CTC towns, including parents, teachers, law enforcement personnel, and other interested community members. The trainees identified the dominant risk factors for substance use in their communities, as well as protective factors they found lacking. They then chose two to five evidence-based prevention programs tailored to those risk factors from a list of tested and effective prevention policies and programs provided by CTC.

COMMUNITY-WIDE RISK REDUCTION

At the start of the study, all fifth-grade students in the selected towns were invited to participate. The participants who contributed data to the study were 4,407 children from 88 schools whose parents consented to their participation. Of this group, 55 percent came from CTC communities and 45 percent from control communities. Just after joining the study and then annually through eighth grade, the students responded to a questionnaire about risk factors and behaviors. The grade 8 assessments occurred 2 years and 8 months after the CTC

One CTC Community's Experience

"CTC provided a framework—a system, a set of steps—to help guide community-wide decisionmaking," explains Ms. Dalene Dutton, the executive director of the Five Town Communities That Care (CTC) program in Maine. "It led us through the process of how to find out what's really going on in our community, how to come together, and how to make decisions about what the community needs based on sound data and scientific principles."

One of the main risk factors identified by the coalition in the Five Town CTC program was the prevailing attitudes in the community, which did not discourage underage use of alcohol, tobacco, and other drugs. To address this risk factor, the Five Town CTC implemented an evidence-based prevention program, called Life Skills Training, in the schools. It teaches children ways to resist social pressures to smoke, drink, and use drugs. Compared with assessments before the program began, 35 percent fewer eighth-grade students reported perceiving laws and norms as favorable to drug use after completing the training.

"We also implemented other activities in the community to make sure that adults are communicating healthy beliefs and clear standards whenever they can," explains Ms. Dutton. "Once you make sure you have a program in place in the area of highest risk, CTC has you look for other places where you can also apply pressure in the community to reduce risk."

The reduction in risk will be much greater, Ms. Dutton says, if the kids get the message from the schools, their parents, their peers, and their church. "CTC allows you to have that stronger effect because you have a broad-based community coalition," she says.

The Five Town CTC also identified and bolstered protective factors for drug use, such as community recognition of socially positive activities. "Kids were telling us that adults were noticing when they were doing wrong but weren't really noticing when they were doing good things," says Ms. Dutton. To address this deficit, the community implemented a program called Skills Training and Recognition (STAR). STAR provides youth with the opportunity to learn new skills, gain recognition as they master the skills, and develop ties to places in the community where they can use their new skills. The researchers measured a 58 percent increase in community recognition of socially positive behavior in middle school students, as assessed by the student surveys.

"That's a really profound impact," says Ms. Dutton, "and we started seeing it soon after implementing the program."

A Webcast featuring communities that implemented the program in the Community Youth Development Study is available at *http://www.drugabuse.gov/newsroom/09/townhall.html*.

communities began the prevention programs that they had selected.

The results of the grade 8 student interviews revealed that since seventh grade, youths in the CTC communities were 32 percent less likely than those in the control towns to have begun using alcohol, 33 percent less likely to have smoked a first cigarette, and 33 percent less likely to have initiated use of smokeless tobacco. Students in CTC communities were also 25 percent less likely to have committed their first delinquent act between grades 7 and 8.

EIGHTH-GRADE STUDENTS IN THE CTC COMMUNITIES WERE LESS LIKELY TO HAVE ENGAGED IN RISKY BEHAVIORS

	CTC Intervention Group	Control Group
Used alcohol in past 30 days	16.4%	21.4%
Had five or more drinks in a row in the past 2 weeks	5.7%	9.0%
Used smokeless tobacco in past 30 days	2.2%	4.3%
Mean number of delinquent acts in past year	0.78	1.13

In CTC communities, eighth-grade students were less likely to report having used alcohol or smokeless tobacco during the 30 days immediately before being interviewed or having participated in binge drinking during the past 2 weeks. CTC communities also experienced significant improvements in their targeted risk and protective factors.

"This study shows that a coalition of community stakeholders armed with tools solidly grounded in the advances in prevention science over the past 30 years can prevent kids from starting and continuing risky behaviors," says Dr. Hawkins.

"These results are very encouraging and support the theory that scaling up effective preventive programs in communities can improve outcomes for youth," says Dr. Belinda Sims of NIDA's Division of Epidemiology, Services and Prevention Research. "We know from other research that even though we have a number of evidence-based preventive interventions focused on drug abuse and related problems, the adoption and implementation of those interventions by communities still lag behind. Systems like CTC may help to reduce this research-to-practice gap."

"Community prevention programs work," says NIDA Director Dr. Nora D. Volkow. "We've also seen that they're cost-effective: For every dollar that is spent, you're going to save 5 to 10 dollars in consequences. But more important, you're going to gear the lives of young people to be successful."

To measure the sustainability of the effects of CTC, Dr. Hawkins and colleagues plan to track the participating youngsters from all 24 communities for 1 year beyond high school. They will also note whether the communities sustain their prevention programs and will examine the effects of ongoing efforts in the CTC communities on youth just entering the target grade levels.

The Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Prevention has made the CTC materials available for free (*http://www.communitiesthatcare.net*). ■

SOURCE

Hawkins, J.D., et al. Results of a type 2 translational research trial to prevent adolescent drug use and delinquency: A test of Communities That Care. *Archives of Pediatrics & Adolescent Medicine* 163 (9):789–798, 2009.

Dr. Paul Kenny Receives the 2010 Waletzky Memorial Award

Dr. Paul Kenny, associate professor in the Department of Molecular Therapeutics on the Florida campus of The Scripps Research Institute, is the recipient of the 2010 Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism. He accepted the award and delivered the keynote lecture at NIDA's "Frontiers in Addiction Research" miniconference in San Diego on November 12, 2010.

Dr. Kenny's research focuses on the molecular underpinnings of addiction. In two recent animal studies, Dr. Kenny and colleagues described how a tiny molecule called microRNA-212 plays a role in determining vulnerability to cocaine addiction. The findings reveal new molecular regulators that control cocaine's impact on the brain's reward pathways and offer a new direction for the development of anti-addiction therapies. Several scientists have hypothesized that microRNAs may influence neuropsychiatric disorders, but Dr. Kenny's team is in the vanguard of examining their impact on addiction.

In another recent animal study led by Dr. Kenny, researchers found indications that strikingly similar molecular mechanisms may underlie compulsive eating and drug addiction. Although the research is in an early stage, it suggests that the techniques and approaches of addiction science may help advance the study of obesity.

The $25,000 award is presented each year to a young scientist who obtained a doctoral degree within the previous 15 years; it is intended to reward and encourage innovative research into the neurobiology of drug addiction and alcoholism. The Waletzky family established the award in 2003 in memory of Jacob P. Waletzky, who died at age 29 of cocaine-induced cardiac arrhythmia.

Two NIDA Grantees Receive Sarnat Prize

Two prominent addiction scientists—Dr. Eric J. Nestler and Dr. Charles P. O'Brien—received the 2010 Rhoda and Bernard Sarnat International Prize in Mental Health. The Institute of Medicine presented the prize to Drs. Nestler and O'Brien at its annual meeting in Washington, D.C., in October. Both researchers are NIDA grantees.

Dr. Nestler, chair of the department of neuroscience and director of the Friedman Brain Institute at Mount Sinai School of Medicine in New York City, has been instrumental in revealing how drugs affect the brain at the molecular level. His laboratory has identified many proteins and genes involved in drugs' effects on the brain's reward regions and demonstrated how drugs rewire the brain's normal reward responses. Dr. Nestler recognized that the brain's reward pathways also play an important role in stress-related disorders such as depression. He also developed a novel mouse model for depression, which helped establish that long-lasting behavioral abnormalities caused by stress can be reversed by treatment with antidepressants.

Dr. O'Brien, vice chair of psychiatry and director of the Charles O'Brien Center for Addiction Treatment at the University of Pennsylvania School of Medicine, has made many important discoveries and contributions over the past 30 years that have become the standard of care in addiction treatment. These include evidence that symptoms of addiction result from reflexive memories that persist even after a person stops using a drug, that drug use over time conditions automatic responses, and that re-exposure to drug-associated cues activates drug urges. The latter discovery has led to behavioral therapies designed to prevent relapse by diminishing conditioned reactions. Dr. O'Brien led the team that first demonstrated the effectiveness of outpatient detoxification for alcoholics and paved the way for outpatient treatment to become the norm; he also led pivotal research pioneering the use of naltrexone as a treatment for alcohol dependence. He and colleague Dr. A. Thomas McLellan developed the Addiction Severity Index, used worldwide to determine the extent of patients' problems and tailor appropriate treatment approaches.

The Sarnat Prize, consisting of a medal and $20,000, is awarded to individuals, groups, or organizations that have demonstrated outstanding achievement in improving mental health.

NIDA Offers Online Training for International Community

Free training courses on addiction and drug abuse research are available to anyone with Internet access, courtesy of NIDA's International Program. The program supports the development and testing of online educational modules for addiction professionals around the globe. Researchers and clinicians in the United States will also find the courses useful; upon completion, they can earn continuing medical education credits. The offerings include:

- Biostatistics for Drug and Substance Abuse Research
- Evaluating Drug and Substance Abuse Programs
- Designing and Managing Drug and Substance Abuse Clinical Trials
- Neurobiology of Addiction

Clinicians, scientists, community-based organizers, policymakers, and public health officials can access these courses—which include self-assessment questions, practical examples, links to resources, and with payment of a modest fee, printable copies of the course materials—at *http://www.DrugAbuseResearchTraining.org*. ■

Teenage Marijuana Use Is on the Rise

A growing percentage of students in the 8th, 10th, and 12th grades are using marijuana on a regular basis, according to the 2010 Monitoring the Future (MTF) survey. Most notably, daily marijuana use increased by more than 10 percent in all three grades since the 2009 survey.

Driven by the rise in marijuana use, illicit drug usage among teenagers has increased overall in the past 3 years. Rates of past-year illicit drug use in 2010 were 16 percent in the 8th grade, 30 percent in the 10th grade, and 38 percent in the 12th grade. The findings, presented at a December 2010 press conference, corroborate the results of the National Survey on Drug Use and Health, released last September (*NIDA Notes*, Volume 23, Number 3, page 19).

The MTF survey also found that ecstasy use, though much lower than marijuana use, increased in 2010, and a long-term decline in cigarette smoking that had been documented in past MTF surveys has leveled off. Alcohol use, however, has fallen to the lowest levels in the history of the survey.

The recent rise in marijuana use follows a 10-year period of decline. In 2010, 1.2 percent of 8th-graders, 3.3 percent of 10th-graders, and 6.1 percent of 12th-graders reported daily marijuana use—defined as 20 or more occasions in the past 30 days. Rates on all measures (daily, past-month, past-year, and lifetime use) increased over the previous year when data for all three grades were combined. In addition, past-month marijuana use among 12th-graders (21.4 percent) surpassed past-month cigarette smoking (19.2 percent).

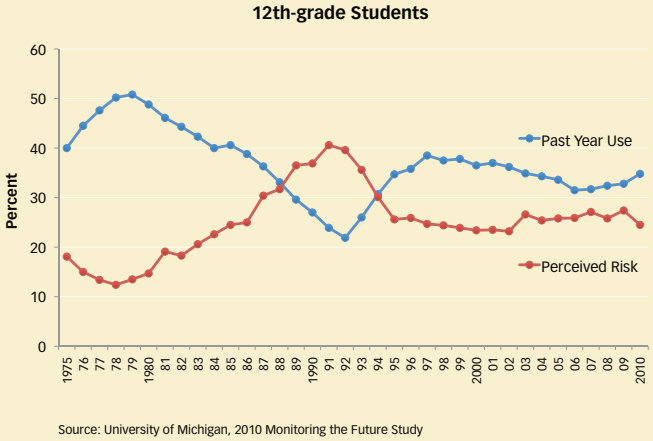
Marijuana use not only places teens at risk of addiction but also impairs their memory, judgment, and ability to learn, says NIDA Director Dr. Nora D. Volkow. "Do we want to jeopardize their future achievement due to exposure to marijuana?" she asks. Eighth-graders, the youngest group surveyed, are especially vulnerable to the drug's harmful effects, she adds, yet in 2010 they reported increases in daily, past-month, and past-year use.

Since the mid-1970s, whenever 12th-graders report a heightened perception of the risks associated with using marijuana, their use of the drug has declined; conversely, when their perception of risk diminishes, their use increases. Dr. Volkow speculates that the recent increase in teen use may be caused by the "attention that the potential use of marijuana as a medication has generated," contributing to an under-appreciation of the harm associated with the drug, and she calls for new research in this area.

ECSTASY MAKES A COMEBACK

Ecstasy use rose in 2010 for the first time in nearly a decade. Use of the drug took off in the late 1990s, peaked in 2001, plummeted immediately afterward, and then leveled off. Dr. Lloyd Johnston of the University of Michigan, the survey's principal investigator, says the revival of interest in ecstasy is due to "generational forgetting"—the current generation of teens is unaware of the drug's harmful effects and so is willing to try it. Use rates rose from 1.3 percent in 2009 to 2.4 percent in 2010 among 8th-graders and from 3.7 percent to 4.7 percent among 10th-graders; there was, however, no increase in use among 12th-graders during this time span. In 2009, Dr. Johnston had predicted that an increase was likely because MTF surveys over the past several years showed a softening of perceived risk (*NIDA Notes*, Volume 23, Number 2, page 19).

INCREASES IN MARIJUANA USE CORRESPOND TO DECLINES IN RISK PERCEPTION Over the past 35 years, the percentage of 12th-grade students reporting past-year marijuana use has shown ups and downs. Such use has risen when risk perception falls and has fallen when risk perception rises.



Source: University of Michigan, 2010 Monitoring the Future Study

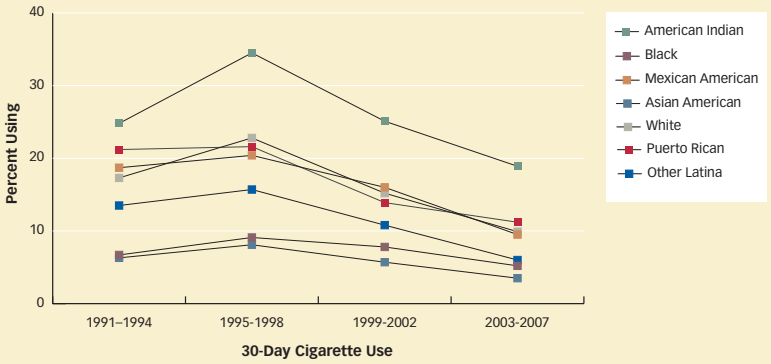
The 2010 findings for other substances include:

- **Alcohol**. A long-term decline continued; past-month use for the three grades combined fell to 26.8 percent, from 28.4 percent in 2009.
- **Prescription and over-the-counter medications.** The only significant change in past-year nonmedical use occurred for Vicodin, a narcotic pain reliever, which fell to 8 percent among 12th-graders, from 9.7 percent in 2009. There was no change in past-year nonmedical use by 12th-graders of the pain reliever OxyContin (5.1 percent); of Adderall (6.5 percent) and Ritalin (2.7 percent), which are prescribed mostly to treat attention deficit hyperactivity disorder; or of over-the-counter cough and cold medicines (6.6 percent).

The 2010 survey covered 46,482 students in 396 public and private schools across the contiguous 48 States. Further information on the survey is available at *http://www.drugabuse.gov/drugpages/MTF.html* and at *http://www.monitoringthefuture.org*. ■

WHAT THE NUMBERS SAY

Fewer Girls Are Smoking, But Change Is Uneven



Rates of cigarette smoking among girls in the eighth grade rose during the early 1990s but then fell sharply between 1995 and 2007. However, racial and ethnic differences persist. Smoking during the past 30 days was highest among American Indian girls and lowest among girls who are black, Asian American, and Latina (but not Mexican American or Puerto Rican). Low socioeconomic status was linked with girls' increased risk of smoking, independent of race and ethnicity.

Source: Analyses of data from about 36,000 girls who participated in the University of Michigan's Monitoring the Future study reported in Wallace, J.M., Jr., et al. Race/ethnicity, socioeconomic factors, and smoking among early adolescent girls in the United States. *Drug and Alcohol Dependence* 104 Supplement 1:S42–S49, 2009.

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